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### **REMARKS**

Applicants request entry of this amendment and reconsideration of the rejection of the claims. Claims 30-49 are pending in the application.

Claims 30, 33, 39, 41, and 43 have been amended to clarify the subject matter of the claims. Applicants submit these amendments are supported throughout the specification including at page 21, lines 17-30, and page 31, lines 1-29. Applicants submit that these amendments do not raise any issues of new matter.

### **Oath/Declaration**

The Examiner has requested a new oath or declaration that lists all of the inventors, to prevent any uncertainty over the inventive entity caused by the earlier filing of two separate declarations in this application. Applicants note that an oath and declaration was filed on May 2, 1997 in parent application Ser. No. 08/850,058 filed May 2, 1997 identifying four inventors: Robert Arathoon, Paul J. Carter, Anne M Merchant, and Leonard G. Presta. In that declaration, one of the inventors, William Robert Arathoon, added in handwriting a W. before the typewritten Robert Arathoon and signed the declaration W.R. Arathoon. The second oath or declaration was filed at the time of filing the instant application, August 12, 1999, to correct the typewritten name of one of the inventors from Robert Arathoon to William Robert Arathoon and did not name the other three inventors. As such, the second declaration is a defective oath and declaration and should be disregarded. Applicants note that there was a typographical error in the original declaration in the typing of the name Robert Arathoon and request correction of his name to W. Robert Arathoon in accord with MPEP 605.04 (b).

### **Specification**

The Examiner objected to the specification, stating that text is missing from the top of "Appendix 1-15" due to holes punched at the top of the pages. The Examiner also objected to the placement of the Appendix directly following the phrase "What is claimed is:".

Applicants have cancelled "Appendix 1-15" and submitted Table 6.1-6.15 on fifteen pages having a larger top margin. The word "Appendix" and the original page number on each page of the original appendix are deleted and "Table 6.X" is inserted therefore, where "X" refers to subpart 1-15 of Table 6. Table 6 has been inserted at page 103, line 16.

The word "Appendix" occurs only once in the originally filed specification at page 96, line 20. The word "Appendix" has been deleted from the specification and the term "Table 6.1-6.15" has been inserted therefore. No new matter is added by these amendments. Withdrawal of these objections is respectfully requested.

### **35 U.S.C. § 112**

Claims 30-49 stand rejected under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended claims 33, 39, 41 and 43 to clarify the subject matter of the claims. Applicants submit the amendments to the claims address the Examiner's rejection.

The Examiner stated that claim 30 is indefinite because it is drawn to a method for making multispecific antibodies that comprise at least two peptides, but the method steps appear drawn to methods where the host cell comprises a nucleic acid that encodes the two or

more polypeptides as one molecule instead of two separate molecules. Applicants respectfully traverse this rejection. It is known and described in the specification that a single nucleic acid can encode one or more polypeptides and that can each be expressed as separate molecules with separate signal sequences and transcription termination sequences. See page 56, lines 26-29. In light of the specification, Applicants submit that claim 30 is not indefinite.

Applicants request withdrawal of the rejection of the claims on this basis.

### **35 U.S.C. § 102**

Claims 30-32, 37, 40, and 41 were rejected under 35 U.S.C. § 102 as being anticipated by Carter (WO 93/06217). The Examiner stated that the phrase "a common sequence" of the light chains as recited in claim 30 is broadly interpreted to even encompass light chains that have only one amino acid sequence in common. The Examiner further stated that Carter teaches methods for making bifunctional F(ab')<sub>2</sub> antibodies comprising domains comprising cysteinyl residues as multimerization domains, and thus teaches methods and host cells that are the same as that claimed. Applicants respectfully traverse this rejection.

Independent claim 30 as amended recites that the variable light chains of the first and additional polypeptides have at least 80% sequence identity. In addition, claim 30 recites that the multispecific antibody is recovered from the host cell culture.

The Carter et al reference does not disclose a multispecific antibody with light chains having at least 80% sequence identity. The Examiner's attention is called to page 21, lines 17-30 of the application, where it is stated that useful light chains from the compared panels

of the present invention are those having amino acid sequence identities of at least 80%, preferably at least 90%, more preferably at least 95%, and most preferably 100% identity.

The Carter et al reference discloses a bispecific antibody with two different light chains.

The Carter et al. reference does not anticipate Applicants' claimed invention because it does not disclose all of the elements of the claims. Applicants submit that Carter does not teach that the light chains of the disclosed antibodies have a common light chain sequence as defined in the present application, i.e., wherein the common light chain sequence has at least 80% sequence identity. Applicants respectfully submit, for at least this reason that claim 30 is not anticipated by Carter. Since claims 31-32, 37, 40, and 41 each depend from, and add additional limitation to, claim 30, these claims are also patentable over Carter. Withdrawal of this rejection is respectfully requested.

Claims 30, 31, 37, 40, 41, and 42 stand rejected under 35 U.S.C. 102(b) as being anticipated by Tso (WO/93/11162). The Examiner stated that the phrase "a common sequence" of the light chains as recited in claim 30 is broadly interpreted to even encompass light chains that have only one amino acid sequence in common. The Examiner further stated that Tso teaches methods for making bispecific antibodies that comprise leucine zipper motifs as multimerization domains, and also teaches host cells and mammalian cells, and thus teaches the methods and host cells of the claims. Applicants respectfully traverse this rejection.

As stated above, as recited in independent claim 30 the variable light chain sequences have at least 80% amino acid sequence identity. Applicants submit that Tso does not disclose that the light chains have at least 80% sequence identity. Applicants respectfully submit that, for at least this reason, claim 30 is not anticipated by Tso. Since claims 31, 37,

40, 41, and 42 each depend from, and add additional limitations to, claim 30, these claims are also patentable over Tso. Withdrawal of this rejection is requested.

Claims 30-42 stand rejected under 35 U.S.C. 102(e) as being anticipated by Carter (U.S. Pat. No. 5,731,168). The Examiner stated that the phrase "a common sequence" of the light chains as recited in claim 30 is broadly interpreted to even encompass light chains that have only one amino acid sequence in common. The Examiner further asserted that Carter teaches methods for making multispecific antibodies and immunoadhesins, as well as host cells that are the same as those claimed. Applicants respectfully traverse this rejection.

As stated above, as recited in independent claim 30, variable light chains have at least 80% amino acid sequence identity. Applicants submit that Carter nowhere discloses light chains that have at least 80% sequence identity. Applicants respectfully submit that for at least this reason, Carter et al do not anticipate claim 30. Since claims 31- 42 each depend from, and add additional limitations to, claim 30, these claims are also patentable over Carter. Withdrawal of this rejection is requested.

### **35 U.S.C. § 103**

Claims 30-49 stand rejected under 35 U.S.C. § 103 as being unpatentable over Vaughan in view of Bosslet and further in view of either Ridgeway, Carter (U.S. Pat. No. 5,807,706), or Carter (WO 96/27011). In the Office Action, the Examiner concluded that it would have been obvious to make a bispecific antibody as taught by Bosslet using the identical light chains of Vaughan, and comprising the multimerization domains of Ridgeway, Carter (U.S.) or Carter (WO) such that the claims of the present invention are rendered obvious. Applicants respectfully traverse this rejection.

Independent claims 30 and 43 of the present invention recite a method of preparing a multispecific antibody comprising a first polypeptide and at least one additional polypeptide, wherein the first polypeptide comprises an interface that interacts with an interface of the additional polypeptide. Claim 30 as amended further provides that the first and additional polypeptides each comprise a binding domain comprising a light chain, wherein the variable light chains have at least 80% sequence identity. Claim 43 further provides selecting a light chain encoding nucleic acid sequence, wherein the light chain is meant to associate with the binding region of each first and additional polypeptide of the multispecific antibody.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) suggestion or motivation to, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; and 3) a reasonable expectation of success. Applicants submit that all of these requirements have not been met because, in the least, there is no motivation to combine or modify the references to obtain the claimed invention.

The Vaughan et al. reference discloses and is directed to a scFv phage library of naïve antibody variable domains. The reference reports that the same light chain is sometimes paired with different heavy chains in antibodies with different specificities. However, this reference does not teach or suggest that such light chains should be selected over other light chains or that these light chains can or should be used in bispecific antibodies. In addition, Vaughan et al. does not describe the use of multimerization domains.

The deficiency of the Vaughan et al. reference is not remedied by reference to Bosslet et al. The Bosslet et al. reference is directed to bispecific and oligospecific mono and

oligovalent receptors. This reference describes the fusion of F(ab) fragments of antibodies of different specificities by means of linkers. The Bosslet et al. reference does not teach or suggest formation of bispecific and oligospecific receptors with a common light chain. In addition, the Bosslet et al. references does not discuss or suggest the use of multimerization region in a polypeptide to form a bispecific or oligospecific receptor.

The Carter et al. references (U.S. Patent No. 5,807,706; WO 96/27011) and the Ridgeway et al. reference are directed to forming heteromultimers with a multimerization region. These references do not teach or suggest a heteromultimer with a common light chain. The Ridgeway reference is directed to an antibody/ immunoadhesin bispecific molecule and common light chains are not found in this type of bispecific molecule. The Carter et al references are directed to forming a multimerization domain and do not teach or suggest a common light chain for a bispecific antibody.

Therefore, Applicants submit that there would be no motivation to combine or modify the references as cited by the Examiner. The Vaughan et al. reference describes the occurrence of the same light chain in scFvs of different specificities in a phage display library but does not teach or suggest the selection of a common light chain over other light chains for use in a bispecific antibody. The Bosslet reference also does not describe using a common light chain in an oligospecific receptor but rather is directed to fusing F(ab)s of two different specificities. Finally, the Carter et al. and Ridgeway references concern the formation of heteromultimers using a multimerization region and also do not describe using a common light chain. Therefore, there would be no motivation to combine or modify these references to achieve Applicants' claimed invention.



Applicants respectfully submit the Examiner is improperly using hindsight reconstruction. As the Federal Circuit stated in In re Fine "we cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention." (In re Fine 837 F2d 1071, 1075 (Fed. Circ. 1998)). As in the In re Fine case, the examiner is picking and choosing isolated disclosures and has not established a suggestion, teaching or motivation to combine these references.

Thus, Applicants respectfully request withdrawal of the 35 U.S.C. §103 rejection of these claims.

#### **Summary**

Applicants submit that all pending claims are in condition for allowance, and notice to that effect is earnestly requested. The Examiner is invited to contact Applicants' representative at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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Dated: March 17, 2003

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## **MARKED-UP VERSION TO SHOW CHANGES MADE**

### **IN THE SPECIFICATION**

The paragraph beginning at page 95, line 29 has been amended as follows:

A large human single chain Fv (scFv) antibody library (Vaughan et al. (1996), supra) was panned for antibodies specific for eleven antigens including Axl (human receptor tyrosine kinase ECD), GCSF-R (human granulocyte colony stimulating factor receptor ECD), IgE (murine IgE), IgE-R (human IgE receptor  $\alpha$ -chain), MPL (human thrombopoietin receptor tyrosine kinase ECD), MusK (human muscle specific receptor tyrosine kinase ECD), NpoR (human orphan receptor NpoR ECD), Rse (human receptor tyrosine kinase, Rse, ECD), HER3 (human receptor tyrosine kinase HER3/c-erbB3 ECD), Ob-R (human leptin receptor ECD), and VEGF (human vascular endothelial growth factor) where ECD refers to the extracellular domain. The nucleotide sequence data for scFv fragments from populations of antibodies raised to each antigen was translated to derive corresponding protein sequences. The V<sub>L</sub> sequences were then compared using the program "align" with the algorithm of Feng and Doolittle (1985, 1987, 1990) to calculate the percentage identity between all pairwise combinations of chains (Feng, D.F. and Doolittle, R.F. (1985) J. Mol. Evol. 21:112-123; Feng, D.F. and Doolittle, R.F. (1987) J. Mol. Evol. 25:351-360; and Feng, D.F. and Doolittle, R.F. (1990) Methods Enzymol. 183:375-387). The percent sequence identity results of each pairwise light chain amino acid sequence comparison were arranged in matrix format (See [Appendix] Table 6.1 - 6.15).

### **IN THE CLAIMS**

30. (AMENDED) A method of preparing a multispecific antibody comprising a first polypeptide and at least one additional polypeptide, wherein

(a) the first polypeptide comprises a multimerization domain forming an interface positioned to interact with an interface of a multimerization domain of the additional polypeptide,

(b) the first and additional polypeptides each comprise a binding domain, the binding domain comprising a heavy chain and a light chain, wherein the variable light chains of the first and additional polypeptides [comprise a common sequence] have at least 80% sequence identity, the method comprising the steps of:

(i) culturing a host cell comprising nucleic acid encoding the first polypeptide and additional polypeptide, and the variable light chain, wherein the culturing is such that the nucleic acid is expressed; and

(ii) recovering the multispecific antibody from the host cell culture.

33. (AMENDED) The method of claim 30 wherein the multimerization domains of the first and additional polypeptides comprise a protuberance-into-cavity interaction, wherein the method further comprises:

generating a protuberance by altering the original nucleic acid encoding the first polypeptide to encode the first polypeptide with an import residue having a larger side chain volume than the original residue, and

generating a cavity by altering a portion of the original nucleic acid encoding the additional polypeptide to encode the additional polypeptide with an import residue having a smaller side chain volume than the original residue.

39. (AMENDED) The method of claim 30 wherein the antibody [heteromultimer] is a multispecific immunoadhesin.

41. (AMENDED) A host cell comprising nucleic acid encoding the multispecific antibody [heteromultimer] of claim 30 [13].

43. (AMENDED) A method of preparing a multispecific antibody comprising:

(a) selecting a first nucleic acid encoding a first polypeptide comprising an altered amino acid residue in an [the] interface of the first polypeptide, wherein the altered amino acid in the interface is an amino acid from at least one additional polypeptide, [is replaced with an amino acid residue on an additional polypeptide] and selecting at least one additional nucleic acid encoding said at least one additional polypeptide so that the amino acid residue on the additional polypeptide specifically interacts with the altered amino acid residue on the first polypeptide, thereby generating a stable interaction between the first and said additional polypeptides;

(b) selecting a light chain encoding nucleic acid sequence, wherein the light chain is meant to associate with the binding region of each first and additional polypeptide of the multispecific antibody;

(c) introducing into a host cell the first and additional nucleic acids and the light chain-encoding nucleic acid, and culturing the cell so that expression of the first and additional nucleic acids and the light chain-encoding nucleic acid occurs to form [the] a multispecific [bispecific] antibody;

(d) recovering the multispecific antibody from the cell culture.

## Clean Set of Claims After entry of Amendment

30. A method of preparing a multispecific antibody comprising a first polypeptide and at least one additional polypeptide, wherein

(a) the first polypeptide comprises a multimerization domain forming an interface positioned to interact with an interface of a multimerization domain of the additional polypeptide,

(b) the first and additional polypeptides each comprise a binding domain, the binding domain comprising a heavy chain and a light chain, wherein the variable light chains of the first and additional polypeptides have at least 80% sequence identity, the method comprising the steps of:

(i) culturing a host cell comprising nucleic acid encoding the first polypeptide and additional polypeptide, and the variable light chain, wherein the culturing is such that the nucleic acid is expressed; and

(ii) recovering the multispecific antibody from the host cell culture.

31. The method of claim 30, wherein the nucleic acid encoding the first polypeptide or the nucleic acid encoding the additional polypeptide, or both, has been altered from the original nucleic acid to encode the interface or a portion thereof.

32. The method of claim 31 wherein the multimerization domains of one of the first or additional polypeptides, or both, are altered to comprise a free thiol-containing residue which is positioned to interact with a free thiol-containing residue of the interface of the other of the first or additional polypeptide such that a disulfide bond is formed between the first and additional polypeptides, wherein the nucleic acid encoding the first polypeptide has been altered from the original nucleic acid to encode the free thiol-containing residue or the nucleic acid encoding the additional polypeptide has been altered from the original nucleic acid to encode the free thiol-containing residue, or both.

33. The method of claim 30 wherein the multimerization domains of the first and additional polypeptides comprise a protuberance-into-cavity interaction, wherein the method further comprises:

generating a protuberance by altering the original nucleic acid encoding the first polypeptide to encode the first polypeptide with an import residue having a larger side chain volume than the original residue, and

generating a cavity by altering a portion of the original nucleic acid encoding the additional polypeptide to encode the additional polypeptide with an import residue having a smaller side chain volume than the original residue.

34. The method of claim 33, wherein the steps of generating a protuberance or generating a cavity, or both, occurs by phage display selection.

35. The method of claim 33 wherein the import residue having a larger side chain volume than the original residue is selected from the group consisting of arginine (R), phenylalanine (F), tyrosine (Y), tryptophan (W), isoleucine (I) and leucine (L).

36. The method of claim 33 wherein the import residue having a smaller side chain volume than the original residue is selected from the group consisting of glycine (G), alanine (A), serine (S), threonine (T), and valine (V), and wherein the import residue is not cysteine (C).

37. The method of claim 30 wherein the first and additional polypeptide each comprise an antibody constant domain.

38. The method of claims 37 wherein the first and additional polypeptide each comprise an antibody constant domain selected from the group consisting of a C<sub>H</sub>3 domain and an IgG.

39. The method of claim 30 wherein the antibody is a multispecific immunoadhesin.

40. The method of claim 30 wherein step (i) is preceded by a step wherein the nucleic acid encoding the first and additional polypeptide is introduced into the host cell.
41. A host cell comprising nucleic acid encoding the multispecific antibody of claim 30.
42. The host cell of claim 41 wherein the host cell is a mammalian cell.
43. A method of preparing a multispecific antibody comprising:
- (a) selecting a first nucleic acid encoding a first polypeptide comprising an altered amino acid residue in an interface of the first polypeptide, wherein the altered amino acid in the interface is an amino acid from at least one additional polypeptide, and selecting at least one additional nucleic acid encoding the at least one additional polypeptide so that the amino acid residue on the additional polypeptide specifically interacts with the altered amino acid residue on the first polypeptide, thereby generating a stable interaction between the first and said additional polypeptides;
  - (b) selecting a light chain encoding nucleic acid sequence, wherein the light chain is meant to associate with the binding region of each first and additional polypeptide of the multispecific antibody;
  - (c) introducing into a host cell the first and additional nucleic acids and the light chain-encoding nucleic acid, and culturing the cell so that expression of the first and additional nucleic acids and the light chain-encoding nucleic acid occurs to form a multispecific antibody;
  - (d) recovering the multispecific antibody from the cell culture.

44. The method of claim 43, wherein at least one of the first and additional nucleic acids of step (a) are altered from the original nucleic acid to encode an amino acid in the interface that interacts with an amino acid of the first or additional amino acid residue thereby generating the stable interaction.

45. The method of claim 44 wherein the altering comprises generating a protuberance-into-cavity interaction at the interface between the first and additional polypeptides.

46. The method of claim 44 wherein the altering comprises importing a free thiol-containing residue into the first or additional polypeptide or both, such that the free thiol-containing residues interact to form a disulfide bond between the first and additional polypeptides.

47. The method of claim 43 wherein the first and additional polypeptide each comprise an antibody constant domain.

48. The method of claim 47 wherein the antibody constant domain is a C<sub>3</sub> domain.

49. The method of claim 48 wherein the antibody constant domain is from a human IgG.



		1	2	3	4	5	Axl	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Clone		1	2	3	4	5	Axl	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1 Axl.25	-	49	50	81	83	79	83	79	83	46	49	49	90	45	80	46	48	42	43	44	49	50	50	79	49
2 Axl.26		-	98	48	52	47	52	47	52	70	77	71	49	68	47	68	72	57	58	59	71	97	98	47	71
3 Axl.27			-	49	53	48	53	48	53	72	79	73	50	70	48	69	74	59	60	61	73	99	100	48	73
4 Axl.32				-	82	83	83	83	83	48	49	46	85	45	84	44	48	42	42	44	46	49	49	98	48
5 Axl.35					-	77	100	77	100	48	52	52	84	51	78	49	52	46	47	48	52	53	53	80	53
6 Axl.36						-	78	-	78	48	48	47	85	47	99	44	47	42	42	43	47	48	48	81	49
7 Axl.47							-		-	48	52	52	84	51	79	49	52	46	47	48	52	53	53	81	53
8 Axl.51										-	72	64	49	61	48	60	66	57	57	58	64	71	72	47	69
9 Axl.75											-	66	50	60	48	62	65	61	60	63	66	78	79	48	67
10 Axl.78												-	48	85	47	95	90	59	58	61	100	72	73	45	94
11 Axl.80													-	47	85	45	49	43	44	45	48	50	50	84	50
12 Axl.82														-	47	80	83	60	58	62	85	69	70	44	82
13 GCSFR.3.2E.A1															-	44	47	42	42	43	47	48	48	82	49
14 GCSFR.3.2E.D5																-	87	57	56	58	95	68	69	43	90
15 GCSFR.3.2E.D6																	-	60	60	62	90	73	74	47	90
16 GCSFR.3.2E.G5																		-	90	98	59	58	59	42	59
17 GCSFR.3.3E.C4																			-	91	58	59	60	42	58
18 GCSFR.A2																				-	61	60	61	43	61
19 GCSFR.A4																					-	72	73	45	94
20 GCSFR.A5																						-	99	48	72
21 GCSFR.A8																							-	48	73
22 GCSFR.F7																								-	47
23 GCSFR.G3																									-
24 IgE.D8																									
25 IgE.G2																									
26 IgER.1A12																									
27 IgER.1D11																									
28 IgER.1E10																									
29 IgER.MAT2C1G11																									
30 Mpl.01																									
31 Mpl.02																									
32 Mpl.03																									
33 Mpl.04																									
34 Mpl.05																									
35 Mpl.06																									
36 Mpl.07																									
37 Mpl.08																									
38 Mpl.11																									
39 Mpl.12																									
40 Mpl.14																									

TABLE 6.1

41	Mpl.16
42	Mpl.19
43	Mpl.21
44	Mpl.24
45	Mpl.26
46	Mpl.28
47	Mpl.29
48	Mpl.30
49	Mpl.31
50	Mpl.32
51	Mpl.33
52	Mpl.35
53	MusK.01
54	MusK.02
55	MusK.06
56	NpoR.25
57	NpoR.44
58	NpoR.53
59	NpoR.81
60	NpoR.86
61	Rse.01
62	Rse.02
63	Rse.03
64	Rse.04
65	Rse.07
66	Rse.08
67	Rse.15
68	Rse.16
69	Rse.18
70	Rse.20
71	Rse.21
72	Rse.22
73	Rse.23
74	Rse.24
75	Rse.52
76	Rse.53
77	Rse.58
78	Rse.60
79	Rse.61
80	Rse.63
81	her3.1
82	her3.10

## TABLE 6.2

[illegible]

### TABLE 6.3



IqE	25	26	IqER	27	28	29	30	31	32	33	34	35	36	37	38	MPL	40	41	42	43	44	45	46	47	48	49	50	51
24	80	44	48	44	49	49	46	44	46	79	50	100	51	49	79	78	81	81	49	80	80	50	80	43	45	46	47	47
59	47	59	66	58	71	71	58	57	57	47	66	50	76	68	48	43	48	48	68	47	48	70	48	65	72	73	69	63
61	48	61	68	60	73	73	60	59	59	48	68	50	77	70	49	44	49	49	70	48	49	72	49	66	74	75	70	65
44	84	44	46	44	46	46	46	42	45	83	48	81	50	46	83	80	100	100	45	84	83	47	99	45	46	47	47	44
48	78	48	52	48	52	48	48	45	48	78	53	83	55	52	78	76	82	82	51	78	78	53	82	43	46	49	50	51
43	98	43	48	43	47	47	45	43	44	98	47	79	48	47	94	95	83	82	46	99	99	48	82	43	46	47	45	46
48	79	48	52	48	52	48	50	47	49	78	53	83	53	52	78	75	83	82	51	79	78	53	83	47	48	49	49	50
58	48	58	62	57	64	64	57	55	56	48	62	47	74	64	47	44	48	48	65	48	49	63	48	73	80	80	76	60
63	49	63	64	62	66	66	62	58	61	48	64	50	78	68	48	44	49	49	68	48	49	65	49	68	74	75	72	61
61	47	61	80	60	100	100	60	57	59	47	79	50	66	84	48	43	46	46	83	47	48	97	46	61	65	66	65	79
45	85	45	48	45	48	48	47	45	47	85	49	90	52	48	83	84	85	86	47	85	86	49	85	45	47	48	49	47
62	47	62	74	61	85	85	61	56	60	47	74	46	62	75	47	43	45	45	75	47	48	85	45	60	61	62	64	72
43	99	43	48	43	47	47	45	43	44	99	47	80	48	47	95	96	84	83	46	100	100	48	83	43	46	47	45	46
58	44	58	76	57	95	95	57	54	56	44	75	47	63	79	45	41	44	44	79	44	45	92	44	57	60	61	61	61
62	47	62	76	61	90	90	61	58	60	47	76	49	67	79	48	43	48	48	79	47	48	89	48	62	64	65	65	74
98	42	98	59	97	59	59	97	87	98	42	71	43	65	57	42	38	42	42	60	42	42	59	42	52	57	58	59	55
91	42	91	57	90	58	58	90	97	91	42	66	44	64	55	42	38	42	42	57	42	42	58	42	51	57	58	57	52
100	43	100	61	99	61	61	99	88	100	43	72	45	67	59	44	40	44	44	62	43	44	61	44	54	59	60	61	57
61	47	61	80	60	100	100	60	57	59	47	79	50	66	84	48	43	46	46	83	47	48	97	46	61	65	66	65	79
60	48	60	67	59	72	72	60	59	59	48	68	50	77	70	49	44	49	49	69	48	49	71	49	66	73	74	70	65
61	48	61	68	60	73	73	60	59	59	48	68	50	77	70	49	44	49	49	70	48	49	72	49	66	74	75	70	65
43	82	43	45	43	45	45	45	41	44	81	47	79	49	45	81	78	98	97	44	82	81	46	97	44	45	46	46	43
61	49	61	75	60	94	94	60	57	59	49	74	50	67	78	50	45	48	48	79	49	50	93	48	64	70	70	68	73
-	43	100	61	99	61	61	99	88	100	43	72	45	67	59	44	40	44	44	62	43	44	61	44	54	59	60	61	57
-	-	43	48	43	47	47	45	43	44	98	47	80	48	47	94	95	84	83	46	99	99	48	83	43	46	47	45	46
		-	61	99	61	61	99	88	100	43	72	45	67	59	44	40	44	44	62	43	44	61	44	54	59	60	61	57
		-	-	60	80	80	60	55	59	48	85	49	65	94	48	44	46	46	93	48	49	78	46	58	60	60	61	99
		-	-	-	60	60	98	87	99	43	71	45	67	58	44	40	44	44	61	43	44	60	44	53	58	59	60	56
		-	-	-	-	-	60	57	59	47	79	50	66	84	48	43	46	46	83	47	48	97	46	61	65	66	65	79
		-	-	-	-	-	-	87	99	45	75	46	67	61	45	41	46	44	61	45	44	60	46	55	58	59	60	60
		-	-	-	-	-	-	-	88	43	67	44	63	56	43	39	42	40	56	43	42	57	42	51	56	57	55	52
		-	-	-	-	-	-	-	-	44	74	46	68	60	44	42	45	44	60	44	44	59	45	55	57	58	60	58
		-	-	-	-	-	-	-	-	-	47	80	48	47	94	95	83	83	46	99	100	48	82	46	47	45	46	46
		-	-	-	-	-	-	-	-	-	-	50	75	82	47	43	48	48	80	47	48	76	48	64	62	63	66	84
		-	-	-	-	-	-	-	-	-	-	-	51	50	79	78	81	81	50	80	80	50	80	43	46	47	48	47
		-	-	-	-	-	-	-	-	-	-	-	-	-	47	46	50	51	69	48	49	65	50	74	72	73	75	64
		-	-	-	-	-	-	-	-	-	-	-	-	-	-	91	83	46	97	47	48	81	46	62	63	64	64	93
		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	80	81	42	95	96	81	82	42	46	47	47	45
		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100	45	84	83	47	99	45	46	47	47	44

TABLE 6.4

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[illegible]

## TABLE 6.5

[illegible]

**TABLE 6.6**



[illegible]



82	83	82	100	80	44	48	47	83	47	47	47	46	45	94	100	46	43	47	44	45	100	46	100	49	49	44	47	81
46	46	46	45	51	62	48	45	46	64	64	64	75	82	40	45	83	82	76	81	74	45	83	44	73	70	62	64	49
99	100	99	84	77	43	46	44	100	47	47	47	47	46	74	84	47	43	48	45	46	84	47	83	49	48	43	47	80
99	100	99	83	76	44	47	46	100	48	48	48	48	47	78	83	48	43	49	46	47	83	48	83	50	49	44	48	80
48	48	48	47	50	61	48	47	48	65	65	65	88	96	42	47	97	92	90	95	88	47	46	46	82	72	61	65	50
82	83	82	99	80	44	48	46	83	47	47	47	46	45	87	99	46	43	47	44	45	99	98	49	49	44	44	47	80
43	43	43	45	47	54	39	38	43	74	74	74	60	60	45	45	61	62	61	59	60	45	44	44	66	68	54	74	43
46	46	46	46	48	59	46	45	46	99	99	99	66	64	42	46	65	60	67	63	65	46	45	45	66	78	59	99	45
47	47	47	47	49	60	47	46	47	100	100	100	67	65	42	47	66	60	68	64	66	47	46	46	67	79	60	100	46
45	45	45	47	49	61	44	45	45	77	78	78	64	64	43	47	65	61	65	63	64	47	47	47	69	72	61	78	47
46	46	46	44	48	57	44	42	46	58	58	58	72	78	40	44	79	78	73	77	71	44	44	44	68	65	57	58	47
-	99	100	83	76	42	45	43	99	47	47	47	47	46	73	83	47	43	48	45	46	83	47	82	49	48	42	47	79
-	-	99	84	77	43	46	44	100	47	47	47	47	46	74	84	47	43	48	45	46	84	47	83	49	48	43	47	80
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-	-	-	-	81	44	48	46	84	47	47	47	46	45	88	100	46	43	47	44	45	100	46	99	49	49	44	47	81
-	-	-	-	-	46	44	42	77	49	49	49	49	48	71	81	49	46	49	47	47	81	49	80	52	51	46	49	81
-	-	-	-	-	-	49	48	43	59	60	60	60	60	40	44	61	54	61	59	59	44	61	43	64	59	100	60	44
-	-	-	-	-	-	-	94	46	46	47	48	48	47	41	48	48	42	49	47	47	48	47	47	50	47	49	47	45
-	-	-	-	-	-	-	-	44	45	46	46	47	46	41	46	47	43	48	46	46	46	46	46	49	46	48	46	45
-	-	-	-	-	-	-	-	-	47	47	47	47	46	74	84	47	43	48	45	46	84	47	83	49	48	43	47	80
-	-	-	-	-	-	-	-	-	-	100	66	66	66	43	47	66	60	67	64	66	47	66	46	66	78	59	100	46
-	-	-	-	-	-	-	-	-	-	-	67	67	65	42	47	66	60	68	64	66	47	66	46	67	79	60	100	46
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[illegible]

TABLE 6.9

80	81	82	83	84	85	Her3	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	ObR	101	102	103	104	105	106	107
45	81	100	85	51	47	80	48	85	85	46	44	85	46	79	82	48	46	79	100	100	100	100	79	80	100	46	50	78	80
72	48	49	51	92	65	47	74	51	73	75	59	51	73	47	49	75	73	47	49	49	49	47	47	47	49	73	98	46	47
74	49	50	52	94	67	48	76	52	75	61	61	52	75	48	50	77	75	48	50	50	50	48	48	48	50	75	100	47	48
46	100	81	85	49	45	84	46	85	47	44	44	85	47	84	83	45	47	83	81	81	81	83	83	83	81	47	49	82	84
48	82	83	83	54	51	78	50	83	49	48	48	83	49	78	83	51	49	78	83	83	83	77	78	78	83	49	53	76	78
46	83	79	85	49	47	99	46	85	47	43	43	85	47	98	79	45	47	98	79	79	79	97	98	98	79	47	48	96	99
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74	49	49	50	80	63	48	86	50	75	63	63	50	75	48	50	67	75	48	49	49	49	47	47	48	49	75	79	47	48
65	46	49	49	76	80	47	62	49	66	61	61	49	66	47	49	92	66	47	49	49	49	47	47	47	49	66	73	46	47
47	85	90	95	51	47	85	49	95	48	45	45	95	48	86	84	47	48	85	90	90	90	84	85	85	90	48	50	84	85
61	45	45	47	70	73	47	61	47	62	62	62	47	62	47	49	81	62	47	45	45	45	46	46	47	45	62	70	46	47
46	84	80	86	49	47	100	46	86	47	43	43	86	47	99	95	45	47	99	80	80	80	98	98	99	80	47	48	97	100
60	44	46	46	71	75	44	59	46	61	58	58	46	61	44	46	88	61	44	46	46	46	44	44	44	46	61	69	43	44
64	48	48	49	75	75	47	62	49	65	62	62	49	65	47	48	84	65	48	48	48	48	47	47	47	48	65	74	46	44
57	42	42	43	63	58	42	60	43	58	98	98	43	58	42	42	61	58	42	42	42	42	42	42	42	42	58	59	41	42
57	42	43	44	62	56	42	59	44	58	91	91	44	58	42	42	60	58	42	43	43	43	42	42	42	43	58	60	41	42
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65	46	49	49	76	80	47	62	49	66	61	61	49	66	47	49	92	66	47	49	49	49	47	47	47	49	66	73	46	47
73	49	50	52	93	66	48	75	52	74	60	60	52	74	48	50	76	74	48	50	50	50	48	48	48	50	74	99	47	48
74	49	50	52	94	67	48	76	52	75	61	61	52	75	48	50	77	75	48	50	50	50	48	48	48	50	75	100	47	48
45	98	79	83	48	44	82	45	83	46	43	43	83	46	82	81	44	46	81	79	79	79	81	81	81	79	46	48	80	82
70	48	49	51	76	74	49	63	51	70	61	61	51	70	49	50	87	70	49	49	49	49	49	49	49	49	70	73	48	49
59	44	44	45	65	60	43	61	45	60	100	100	45	60	43	44	63	60	43	44	44	44	43	43	43	44	60	61	42	43
46	84	80	86	49	47	99	47	86	47	43	43	86	47	98	94	45	47	98	80	80	80	97	98	98	80	47	48	97	99
59	44	44	45	65	60	43	61	45	60	100	100	45	60	43	44	63	60	43	44	44	44	43	43	43	44	60	61	42	43
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58	44	44	45	64	59	43	60	45	59	99	99	45	59	43	44	62	59	43	44	44	44	43	43	43	44	59	60	42	43
65	46	49	49	76	80	47	62	49	66	61	61	49	66	47	49	92	66	47	49	49	49	47	47	47	49	66	73	46	47
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56	42	44	46	61	54	43	57	46	57	88	88	46	57	43	44	59	57	43	44	44	44	43	43	43	44	57	59	42	43
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46	83	79	85	49	47	99	46	85	47	43	43	85	47	98	94	45	47	98	79	79	79	97	98	98	79	47	48	96	99
62	48	50	49	72	84	47	62	49	63	72	72	49	63	47	49	81	63	47	50	50	50	47	47	47	50	63	68	46	47
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72	50	51	51	79	64	48	78	51	73	67	67	51	73	48	50	69	73	48	51	51	51	48	48	48	51	73	77	47	48
63	46	49	49	71	93	47	63	49	64	59	59	49	64	47	49	81	64	47	49	49	49	47	47	47	49	64	70	46	47
46	83	79	84	50	47	95	46	84	47	44	44	84	47	94	94	46	47	94	79	79	79	93	94	94	79	47	49	92	95
42	80	78	83	45	43	96	44	83	43	43	40	83	43	95	91	42	43	95	78	78	78	94	94	95	78	43	44	93	96
46	100	81	85	49	45	84	46	85	47	47	44	85	47	84	83	45	47	83	81	81	81	83	83	83	81	47	49	82	84

TABLE 6.10

52



46	100	81	84	49	45	83	47	84	47	44	84	47	83	46	47	82	46	81	81	82	82	46	81	47	49	81	83
63	45	49	48	70	92	46	63	48	64	62	48	64	46	80	80	64	48	49	49	46	46	49	64	70	45	46	
46	84	80	86	49	47	100	46	86	47	43	86	47	99	45	47	99	95	80	80	98	99	80	47	48	97	100	
47	83	80	86	50	48	100	48	86	48	44	86	48	99	47	48	99	95	80	80	98	99	80	48	49	97	100	
64	47	50	50	75	77	48	61	50	65	61	50	65	48	90	65	48	50	50	50	48	48	50	65	72	47	48	
46	99	80	84	49	45	83	46	84	47	44	84	47	83	45	47	83	82	80	80	82	82	80	47	49	81	83	
73	45	43	44	68	57	43	68	44	74	54	44	74	43	63	74	43	43	43	43	43	43	43	74	66	42	43	
98	46	45	49	80	59	46	75	49	99	59	49	99	46	71	99	46	45	45	45	46	46	45	99	74	45	46	
99	47	46	50	80	60	47	76	50	100	60	50	100	47	72	100	47	48	46	46	47	47	46	100	75	46	47	
77	47	47	46	72	60	45	74	46	78	61	46	78	45	65	78	45	47	47	47	45	45	47	78	70	44	45	
57	44	47	47	66	98	46	58	47	58	57	47	58	46	77	58	46	47	47	47	46	46	47	58	65	45	46	
46	83	79	85	49	47	99	46	85	47	42	85	47	98	45	47	98	94	79	79	97	98	79	47	48	96	99	
46	84	80	86	49	47	100	46	86	47	43	86	47	99	45	47	99	95	80	80	98	99	80	47	48	97	100	
46	83	79	85	49	47	99	46	85	47	42	85	47	98	45	47	98	94	79	79	97	97	79	47	48	96	99	
46	100	81	85	49	45	84	46	85	47	44	85	47	84	45	47	84	83	81	81	83	83	81	47	49	82	84	
48	81	81	80	52	49	77	46	80	49	46	80	49	77	48	49	77	79	81	81	77	77	81	49	51	75	77	
59	44	44	45	65	60	43	61	45	60	100	45	60	43	63	60	43	44	44	44	43	43	44	60	61	42	43	
46	48	45	48	49	48	46	44	48	47	49	48	47	46	45	47	46	46	45	45	47	46	45	47	47	45	46	
45	46	45	46	48	45	44	45	46	46	48	46	46	44	44	46	44	44	45	45	45	44	45	46	46	43	44	
46	84	80	86	49	47	100	46	86	47	43	86	47	99	45	47	99	95	80	80	98	99	80	47	48	97	100	
99	47	46	50	80	59	47	76	50	100	59	50	100	47	72	100	47	48	46	46	47	47	46	100	75	46	47	
99	47	46	50	80	60	47	76	50	100	60	50	100	47	72	100	47	48	46	46	47	47	46	100	75	46	47	
66	46	46	48	76	73	47	62	48	67	60	48	67	47	82	67	47	46	46	46	47	47	46	67	73	46	47	
65	45	48	48	75	79	46	61	48	65	60	48	65	46	91	65	46	48	48	48	46	46	48	65	72	45	46	
41	88	72	75	44	40	74	41	75	42	40	75	42	74	73	41	42	74	72	72	73	73	72	42	43	72	74	
46	100	81	85	49	45	84	46	85	47	44	85	47	84	45	47	84	83	81	81	83	83	81	47	49	82	84	
65	46	49	49	76	80	47	62	49	66	61	49	66	47	92	66	47	49	49	49	47	47	49	66	73	46	47	
59	43	46	45	72	78	43	58	45	60	54	45	60	43	91	60	43	45	46	46	43	43	46	60	71	42	43	
67	47	47	49	76	74	48	62	49	68	61	49	68	48	83	68	48	49	47	47	48	48	47	68	73	47	48	
64	44	47	47	74	78	45	60	47	64	59	47	64	45	90	64	45	47	47	47	45	45	47	64	71	44	45	
65	45	45	47	75	72	46	62	47	66	59	47	66	46	81	66	46	47	45	45	46	46	45	66	72	45	46	
46	100	81	85	49	45	84	46	85	47	44	85	47	84	45	47	84	83	81	81	83	83	81	47	49	82	84	
65	46	49	49	76	80	47	62	49	66	61	49	66	47	92	66	47	49	49	49	47	47	49	66	73	46	47	
45	99	81	84	48	44	83	46	84	46	43	84	46	83	44	46	83	82	81	81	82	82	81	46	48	81	83	
66	49	51	51	86	70	49	71	51	67	64	51	67	49	77	67	49	51	51	51	49	49	49	79	96	47	48	
78	49	49	52	90	67	48	72	52	79	59	52	79	48	72	79	48	49	49	49	48	48	49	79	96	47	48	
59	44	44	45	65	60	43	61	45	60	100	45	60	43	63	60	43	44	44	44	43	43	44	60	61	42	43	
99	47	46	50	80	60	47	76	50	100	60	50	100	47	72	100	47	48	46	46	47	47	46	100	75	46	47	
45	81	100	85	51	47	80	48	85	46	44	85	46	79	48	46	79	82	80	100	79	80	100	46	50	78	80	
-	46	45	49	80	59	46	75	49	99	59	49	99	46	71	99	46	47	45	45	46	46	45	99	74	45	46	
-	-	81	85	49	45	84	46	85	47	44	85	47	84	45	47	84	83	81	81	83	83	81	47	49	82	84	
-	-	-	85	51	47	80	48	85	46	44	85	46	80	47	46	79	82	82	100	79	80	100	46	50	78	80	

[illegible]

## TABLE 6.12





44	46	84	83	83	44	49	46	83	41	Mpl.16
62	82	48	46	46	62	65	83	48	42	Mpl.19
43	47	86	100	100	43	46	47	85	43	Mpl.21
44	48	86	100	100	44	48	48	85	44	Mpl.24
61	96	50	48	48	61	69	97	51	45	Mpl.26
44	46	84	83	83	44	48	46	82	46	Mpl.28
54	61	44	43	43	54	94	61	47	47	Mpl.29
59	65	49	46	46	59	78	65	50	48	Mpl.30
60	66	50	47	47	60	79	66	51	49	Mpl.31
61	65	46	45	45	61	99	65	48	50	Mpl.32
57	78	47	46	46	57	60	79	49	51	Mpl.33
42	47	85	99	99	42	46	47	84	52	Mpl.35
43	47	86	100	100	43	46	47	85	53	Musk.01
42	47	85	99	99	42	46	47	84	54	Musk.02
44	46	85	84	84	44	48	46	83	55	Musk.06
46	49	80	77	77	46	50	49	78	56	NpoR.25
100	60	45	43	43	99	61	61	46	57	NpoR.44
49	48	48	46	46	49	45	48	49	58	NpoR.53
48	47	46	44	44	48	46	47	48	59	NpoR.81
43	47	86	100	100	43	46	47	85	60	NpoR.86
59	66	50	47	47	59	78	66	51	61	Rse.01
60	66	50	47	47	60	79	66	51	62	Rse.02
60	88	48	47	47	60	65	89	49	63	Rse.03
60	98	48	46	46	60	65	99	49	64	Rse.04
40	41	75	74	74	40	44	41	80	65	Rse.07
44	46	85	84	84	44	48	46	83	66	Rse.08
61	99	49	47	47	61	66	100	50	67	Rse.15
54	94	45	43	43	54	62	95	46	68	Rse.16
61	90	49	48	48	61	66	90	50	69	Rse.18
59	97	47	45	45	59	64	98	48	70	Rse.20
59	88	47	46	46	59	65	88	48	71	Rse.21
44	46	85	84	84	44	48	46	83	72	Rse.22
61	99	49	47	47	61	66	100	50	73	Rse.23
43	45	84	83	83	43	48	45	83	74	Rse.24
64	82	51	49	49	63	70	83	52	75	Rse.52
59	72	52	48	48	59	73	73	53	76	Rse.53
100	60	45	43	43	99	61	61	46	77	Rse.58
60	66	50	47	47	60	79	66	51	78	Rse.60
44	49	85	80	80	44	48	49	85	79	Rse.61
59	65	49	46	46	59	78	65	50	80	Rse.63
44	46	85	84	84	44	48	46	83	81	her3.1
44	49	85	80	80	44	48	49	85	82	her3.10

TABLE 6.14

45	49	100	86	86	45	47	49	99	100	83	her3.11
65	75	53	49	49	64	73	76	54	53	84	her3.12
60	79	48	47	47	60	61	80	49	48	85	her3.16
43	47	86	100	100	43	46	47	85	86	86	her3.18
61	62	47	46	46	60	75	62	49	47	87	her3.19
45	49	100	86	86	45	47	49	99	100	88	her3.22
60	66	50	47	47	60	79	66	51	50	89	her3.3
100	60	45	43	43	99	61	61	46	45	90	her3.4
45	49	100	86	86	45	47	49	99	100	91	her3.7
60	66	50	47	47	60	79	66	51	50	92	obr.1
43	47	87	99	99	43	46	47	86	87	93	obr.11
44	49	85	95	95	44	48	49	83	85	94	obr.12
63	91	49	45	45	63	66	92	51	49	95	obr.14
60	66	50	47	47	60	79	66	51	50	96	obr.15
43	47	85	99	99	43	46	47	84	85	97	obr.16
44	49	85	80	80	44	48	49	85	85	98	obr.17
44	49	85	80	80	44	48	49	85	85	99	obr.18
44	49	85	80	80	44	48	49	85	85	100	obr.19
43	47	85	98	98	43	46	47	83	85	101	obr.2
43	47	86	99	99	43	46	47	85	86	102	obr.20
44	49	85	80	80	44	48	49	85	85	103	obr.21
60	66	50	47	47	60	79	66	51	50	104	obr.22
61	72	52	48	48	60	71	73	53	52	105	obr.23
42	46	85	97	97	42	45	46	83	85	106	obr.24
43	47	86	100	100	43	46	47	85	86	107	obr.26
-	60	45	43	43	99	61	61	46	45	108	obr.3
-	-	49	47	47	60	66	99	50	49	109	obr.4
		-	86	86	45	47	49	99	100	110	vegf.1
			-	100	43	46	47	85	86	111	vegf.10
				-	43	46	47	85	86	112	vegf.2
					-	61	61	46	45	113	vegf.3
						-	66	49	47	114	vegf.4
							-	50	49	115	vegf.5
								-	99	116	vegf.6
									-	117	vegf.8
108	109	110	111	112	113	114	115	116	117		Clone
					VEGF						

TABLE 6.15